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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,292	10/01/2003	Toshihiro Mitaka	1285-7 PCT/CON	7064
23869	7590	09/20/2005	EXAMINER	
HOFFMANN & BARON, LLP 6900 JERICHO TURNPIKE SYOSSET, NY 11791			FERNANDEZ, SUSAN EMILY	
			ART UNIT	PAPER NUMBER
			1651	
DATE MAILED: 09/20/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/676,292

Applicant(s)

MITAKA ET AL.

Examiner

Susan E. Fernandez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 1-10, 12-14, 16-18, 20, 22-24, 26, 28-30, 32 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11, 15, 19, 21, 25, 27, 31 and 33 is/are rejected.
- 7) ☒ Claim(s) 11, 15, 19, 21, 25, 27, 31 and 33 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/03, 6/04, 6/05</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1-34 are pending.

Election/Restrictions

Applicant's election of Group VI, claims 11, 15, 19, 21, 25, 27, 31 and 33, and "CYP3A2" as the gene for both species (a) and (e), in the reply filed on August 22, 2005, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-10, 12-14, 16-18, 20, 22-24, 26, 28-30, 32, and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 11, 15, 19, 21, 25, 27, 31, and 33 are examined on the merits to the extent they read on the elected subject matter.

Claim Objections

Claims 11, 15, 19, 21, 25, 27, 31, and 33 are objected to because of the following informalities: These claims are objected to as depending on non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Applicant is advised that should claim 11 be found allowable, claim 33 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 15, 19, 21, 25, 27, 31, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 15, 19, 21, 25, 27, 31, and 33 are indefinite since claim 5 recites "culturing the small hepatocyte-rich colonies according to claim 1". The phrase, "according to claim 1" implies that claim 1 is a method of culturing small hepatocyte-rich colonies. Since the claims recite claim 5, claims 11, 15, 19, 21, 25, 27, 31, and 33 are rejected under 35 U.S.C. 112, second paragraph.

The term "small" preceding the term "hepatocyte-rich" in claims 11, 19, and 33 is a relative term which renders the claims indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of

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ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, claims 11, 15, 19, 21, 25, 27, 31, and 33 are rejected under 35 U.S.C. 112, second paragraph.

Claim 11 is rendered indefinite by the phrase, "identifying a gene the expression of which is induced or repressed in the cells in the small hepatocyte-rich colonies, and/or determining the expression level thereof". It is not clear that these steps have any relationship to the initial step of contacting colonies that had undergone maturation with a chemical substance. Additionally, it is not clear that "the small hepatocyte-rich colonies" recited in the phrase actually refer to small hepatocyte-rich colonies that had undergone maturation. Thus, claims 11, 15, 21, and 27 are rejected under 35 U.S.C. 112, second paragraph.

Claims 27 and 31 are indefinite since each recites "enzymes" in the second line, whereas the claim is drawn to a drug-metabolizing enzyme gene. CYP3A2 is an enzyme, and a gene encodes this enzyme. Thus, claims 27 and 31 are rejected under 35 U.S.C. 112, second paragraph. The term "enzymes" at the second line of each of these claims should be replaced with "genes".

Claim 33 is indefinite since it recites "the effect of a chemical substance connected with the liver function *in vitro*". This phrase is confusing since it is unclear what is defined by "a chemical substance connected with the liver function *in vitro*". Moreover, it is unclear what effect is estimated, since the phrase does not clearly indicate the estimation of the effect of a chemical substance on another substance or an action. Finally, claim 33 is indefinite since it recites at lines 3-5, "identifying a gene the expression of which is induced or repressed in the cells in the above-described small hepatocyte-rich colonies, and/or determining the expression level thereof". It is not clear that these steps have any relationship to the initial step of

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contacting colonies that had undergone maturation with a chemical substance. Additionally, it is not clear that "the above-described small hepatocyte-rich colonies" recited in the phrase actually refer to colonies that had undergone maturation, or the colonies that had not undergone maturation. Thus, claim 33 is rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 15, 19, 21, 25, 27, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. (US 6,127,117) in view of Sato et al. (Liver, Vol. 19, No. 6, December 1999, pages 481-488), Tateno et al. (Wound Repair and Regeneration, 1999, 7(1): 36-

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44), and Mitaka et al. (Biochemical and Biophysical Research Communications, 1995, 214(2): 310-317).

Morris et al. discloses a method of estimating an effect of chemical substances, specifically xenobiotics, on a liver function *in vitro*, where the liver function is the function of cytochrome P450 enzymes of the liver (column 3, lines 31-37). Note that the cytochrome P450 enzymes of the liver function in the metabolism of drugs and chemicals (column 1, lines 28-32). The method is accomplished by determining whether a xenobiotic induces the expression of a drug-metabolizing enzyme (cytochrome P450) which is present in the liver. In the *in vitro* method, hepatocytes are isolated (column 15, line 35), treated with xenobiotics including PB (phenobarbital) and HC (hydrocortisone-21-hemisuccinate) (see column 16, lines 19-20 and column 11, lines 64-65), and harvested for total RNA or protein in order to perform analysis for measuring RNA and protein level for P450 enzyme expression (column 16, lines 32-35 and lines 43-45). Experiments showed that certain concentrations of HC induced CYP3A2 mRNA expression (column 18, lines 1-5).

Morris et al. does not expressly disclose determining whether a xenobiotic represses the expression of cytochrome P450, nor does it disclose using small hepatocyte-rich colonies that had undergone maturation.

Sato et al. discloses the isolation and culture of a small hepatocyte-rich fraction (page 482, second column, second paragraph). Cultures treated with nicotinamide resulted in the highest number of small hepatocytes per colony (page 485, first column, second paragraph).

Tateno et al. discloses pure fractions of small hepatocytes, pointing out that “interactions with non-parenchymal cells appear to be essential for colony formation of small hepatocytes” (page 43, first column, first full paragraph).

Mitaka et al. disclose the differentiation of small hepatocytes in colonies into mature hepatocytes (page 311, first paragraph). This was accomplished by isolating individual small hepatocytes (page 311, second paragraph, lines 6-8), which were resuspended in fresh medium (page 311, second paragraph, lines 11-12). The cells were then inoculated onto culture dishes coated with an extracellular medium, rat tail collagen (page 311, second paragraph, lines 14-15). Later, the medium was changed to an extracellular matrix-free medium (page 311, second paragraph, lines 16-18).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have used the methods of Mitaka et al. to measure the repressed expression of cytochrome P450. One of ordinary skill in the art would have been motivated to do this since any xenobiotic would either induce, repress, or have no effect on cytochrome P450 expression, and the measurement of reduced expression would not have required any alteration of the methods of Mitaka et al. (except for the testing of other xenobiotics).

Additionally, at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have substituted the hepatocytes used in Morris et al. with the mature hepatocytes obtained from the maturation of small hepatocytes. One of ordinary skill in the art would have been motivated to do this since Mitaka et al. disclose that these mature hepatocytes possess hepatic characteristics (page 310, first paragraph). Therefore, use of these cells would have yielded results which would have closely reflected *in vivo* results.

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Additionally, there would have been a reasonable expectation of success of substituting hepatocytes used in Morris et al. with mature hepatocytes derived from the methods of Mitaka et al. since they would have all possessed functional cytochrome P450. Finally, the methods for maturation, as outlined in claim 5 of the application under examination, are similar to the final culturing steps disclosed in Morris et al. (column 16, lines 11-17). Specifically, hepatocytes are cultured in medium containing Matrigel (an extracellular matrix) and then cultured in Matrigel-free medium.

Finally, one would have been motivated to have used colonies rich with small hepatocytes when performing the maturation steps of Mitaka et al. since this would have resulted in a higher concentration of mature hepatocytes. However, sufficient number of non-parenchymal cells would have had to be have been present in these small hepatocyte-rich colonies in order to ensure culture formation.

Thus, a holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan E. Fernandez
Assistant Examiner
Art Unit 1651

sef



FRANCISCO PRATS
PRIMARY EXAMINER